

## **Testimony for Social Security Administration Meeting on Medical Technologies and Rare Diseases**

**December 4-5, 2007**

**William A. Gahl, MD, PhD and P. Suzanne Hart, PhD  
National Human Genome Research Institute, National Institutes of Health**

**WG:** First, I would like to congratulate the SSA for conducting this hearing into Medical Technologies and Rare Diseases. New and existing medical technologies, whether genetic, biochemical, or radiographic, contribute a measure of objectivity to the diagnosis of a rare disease. In some instances, they carry prognostic value as well.

Dr. Suzanne Hart has extensive experience directing molecular and biochemical genetic diagnostic laboratories, and is currently the Scientific Advisor for The Collaboration, Education, and Test Translation (CETT) Program for Rare Genetic Diseases, which helps bring new genetic tests to patients while encouraging clinical, laboratory, and research collaborations. She will discuss some of the current and future medical technologies available in the areas of molecular and biochemical diagnostics.

**SH:** The Task Force on Genetic Testing, convened by National Institutes of Health-Department of Energy (NIH-DOE) Joint Working Group on the Ethical, Legal and Social Implications (ELSI) of Human Genome Research, defined a genetic test as:

**The analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers, establishing prenatal and clinical diagnosis or prognosis. Prenatal, newborn, and carrier screening, as well as testing in high-risk families, are included. Tests for metabolites are covered only when they are undertaken with high probability that an excess or deficiency of the metabolite indicates the presence of heritable mutations in single genes. Tests conducted purely for research are excluded from the definition, as are tests for somatic (as opposed to heritable) mutations, and testing for forensic purposes.**  
<http://genome.gov/10002405>

Individuals who undergo genetic testing fall into two main categories: 1. symptomatic individuals or those in whom a specific clinical feature, or phenotype, suggests a genetic disorder; or 2. individuals with a family history of a genetic condition.

Current genetic testing methodologies are broadly categorized into biochemical, molecular, and cytogenetic techniques. This testimony will focus on biochemical and molecular techniques.

Existing molecular genetic testing includes targeted mutation analysis (for example by targeted sequencing, allele specific oligonucleotide analysis, etc.), whole gene sequencing (typically covering coding regions and exon/intron splice junctions), determination of number of repeats for trinculeotide repeat disorders, deletion/duplication analysis, and determination of epigenetic changes, such as methylation status. Detection rates vary based upon the gene and the methodology used. As sequencing costs have fallen, full sequencing has become more common; this will likely result in higher detection rates compared to targeted analysis.

In the future, array technology will be more frequently employed in the molecular diagnostic laboratory. There are two main areas where this technology will be helpful. First, for large genes, array technology provides a cost-effective and time saving platform for mutation detection. For example, the dystrophin gene, which is mutated in the two allelic disorders Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy, spans more than 2,000,000 basepairs of DNA. More than 500 deletions, 80 duplications, and almost 1000 single base mutations have been described in this gene. Two arrays have been developed to aid in genetic testing for these muscular dystrophies. The first array detects deletions and duplications of the DMD gene, which account for approximately 70-75% of mutations in DMD and 90-95% of mutations in Becker muscular dystrophy. The second array is a sequencing array that allows the whole DMD gene to be interrogated in a single assay. Another use of array technology will be the evaluation of multiple genes simultaneously. The advantage of this technology can be illustrated with X-linked mental retardation. Currently, 63 genes on the X chromosome are known to be associated with syndromic X-linked mental retardation (i.e., mental retardation with other phenotypic features). An array is under development that would allow analysis of 34 genes on the X chromosome concurrently. At the present time, such analyses would have to be conducted sequentially at a significantly higher cost and turn-around time.

Biochemical testing for rare diseases involves standard blood chemistry, hematological and immunological studies, as well as specialized tests for rare metabolic disorders. These include amino acid and organic acid analysis, enzyme assays, antibody tests, specific small molecule assays, and profiles of abnormal metabolites. As Dr. Howell has mentioned, tandem mass spectrometry is revolutionizing newborn screening, and this method has the potential to improve the biochemical diagnosis of symptomatic patients as well as newborns. The technique can allow faster and perhaps more definitive diagnosis of known diseases, and can reveal new disorders by detecting small molecules that signal disease.

Ultimately, the best testing methodology varies with the disorder or gene involved, and may also depend upon ethnicity. For example, carrier testing for Tay Sachs disease, in the absence of family history, is best performed by molecular means for Ashkenazi Jewish

individuals but by biochemical methods for non-Ashkenazi Jewish individuals. In some cases, combined testing may be the most appropriate approach.

**WG:** Medical technology gets us to a diagnosis. Sometimes diagnosis means absolutely that the patient will be medically fragile or disabled. Examples might include Fragile X syndrome, Tay Sachs disease and other lysosomal storage disorders, adrenoleukodystrophy, Usher's syndrome (predicting deafness), or albinism (predicting blindness). For other diagnoses, additional information is needed to ascertain medical needs or disabilities. Examples would include disorders with onset of symptoms in adulthood, such as Huntington Disease, Hereditary Inclusion Body Myopathy and Fabry disease. Lists of rare diseases could be established to differentiate these types of disorders.

Most patients with a rare disease diagnosis eventually require increased medical intervention and functional support in activities of daily living, but when? This depends upon whether they have symptoms at the time they are genetically tested, or are asymptomatic, with testing performed for other reasons. In the latter case, they may lose function later. Indeed, some disorders are static and some are progressive in their manifestation of symptoms.

New technologies are not likely to change these basic issues, only to expand their applicability to new disorders and to more patients with currently known disorders.

The bulk of the decisions regarding SSA allowance for rare diseases will continue to be made based upon input from health care professionals. For example, members of the Society for Inherited Metabolic Disorders are the country's experts in rare biochemical diseases, and these professionals can provide advice regarding the medical needs and expected disabilities associated with a specific rare disease diagnosis. The SIMD, along with other professional groups, could help create lists of rare diseases that are always associated with disability and that sometimes are associated with dysfunction. This would assist in the adjudicatory process.